Yo-Yo Dieting: Mixed Messages for β-Cell Plasticity

Ke Ma[1,2] and Sangeeta Dhawan[2,3]

Diabetes 2022;71:2253–2255 | https://doi.org/10.2337/dbi22-0024

Weight management in individuals with obesity is a first-line lifestyle intervention to prevent worsening of insulin resistance, progression to type 2 diabetes (T2D), and adverse cardiovascular disease outcome. However, persistent weight reduction is often hard to maintain, with <6% of subjects able to achieve sustained weight loss during a 15-year follow-up (1). Current evidence suggests that repeated weight loss and subsequent gain, a phenomenon known as weight cycling or "yo-yo dieting," exacerbates the risk for T2D and cardiovascular disease (2). The full spectrum of its adverse effects and the underlying mechanisms, however, remain poorly understood.

In this issue of *Diabetes*, Winn et al. (3) reveal a surprising consequence of yo-yo dieting on inducing β-cell maladaptation, leading to impaired insulin secretion mismatched for the insulin-resistant peripheral tissue. This work builds upon the initial discovery of weight cycling–induced worsening of peripheral insulin resistance compared with that of similarly obese mice (4). In an insulin-resistant state, β-cells increase insulin secretion to maintain normoglycemia and compensate for the diminished peripheral insulin action. Persistence of insulin resistance leads to eventual decompensation due to β-cell dysfunction, dedifferentiation, and death (5,6). The most intriguing finding of the current study lies in the islet insulin secretion defects upon weight cycling despite impaired peripheral insulin sensitivity comparable to the persistently obese state. This metabolic conundrum suggests that β-cell–intrinsic defects are uniquely induced by weight cycling and exacerbate decompensation (Fig. 1). These defects do not involve diminished glucose responsiveness but instead entail impaired cAMP-dependent secretion and reduced insulin content. Transcriptomic analysis of islets from obese and weight-cycled mice revealed an upregulated replication-related program and downregulation of genes involved in protein localization, β-cell identity, and functional maturity, indicative of a functionally immature β-cell state primed to replicate. However, no corresponding differences in replication were observed. As attempted replication under conditions of stress can trigger cell death (7,8), β-cells subjected to weight cycling may not be survival competent. This notion is supported by a decrease in islet size and area along with reduced β-cell number. Intriguingly, the authors noted induction of *Ins1* and *Ins2*, a potential compensatory response to attenuated β-cell functional mass. As cell cycle genes are involved in DNA repair, differential gene expression in this pathway may reflect an ongoing DNA damage response. Direct assessment of β-cell DNA damage and cell death preceding and during the weight cycling regimen will clarify the mechanisms that underly β-cell decompensation triggered by nutrient fluctuations.

What, then, are the signals that drive β-cell maladaptation during weight cycling? Body weight fluctuations evoke nutrient fluxes in metabolic tissues along with altered appetite control in the central nervous system (9), which raises the possibility of interorgan cross talk subserving β-cell defects. Adipose tissue bears the brunt of weight cycling as a major site of lipid storage and mobilization, and its heightened proinflammatory T-cell response contributes to impaired glucose tolerance (4). While the authors found that the cause of weight cycling–induced worsening of glucose tolerance largely lies in β-cell insulin secretion defects, they noted reduced glucose uptake in adipose tissue and muscle. This constellation of metabolic abnormalities highlights the complexity of tissue responses to repeated insults of nutritional overload and deprivation. Weight loss and regain leads to lipolysis and fatty acid re-esterification in adipose tissue (10). Nutritional stress due to lipid overload and hyperglycemia induces β-cell adaptation during weight gain, while subsequent weight loss and the accompanying onslaught of lipolytic mediators could trigger a maladaptive response (11). Metabolome and secretome profiling across multiple tissues at distinct stages of

[1]Department of Diabetes Complications and Metabolism, Arthur Riggs Diabetes and Metabolism Research Institute, City of Hope, Duarte, CA
[2]Irell and Manella Graduate School of Biological Sciences, Beckman Research Institute, City of Hope, Duarte, CA
[3]Department of Translational Research and Cellular Therapeutics, Arthur Riggs Diabetes and Metabolism Research Institute, City of Hope, Duarte, CA

Corresponding authors: Ke Ma, kema@coh.org, and Sangeeta Dhawan, sdhawan@coh.org

See accompanying article, p. 2313.

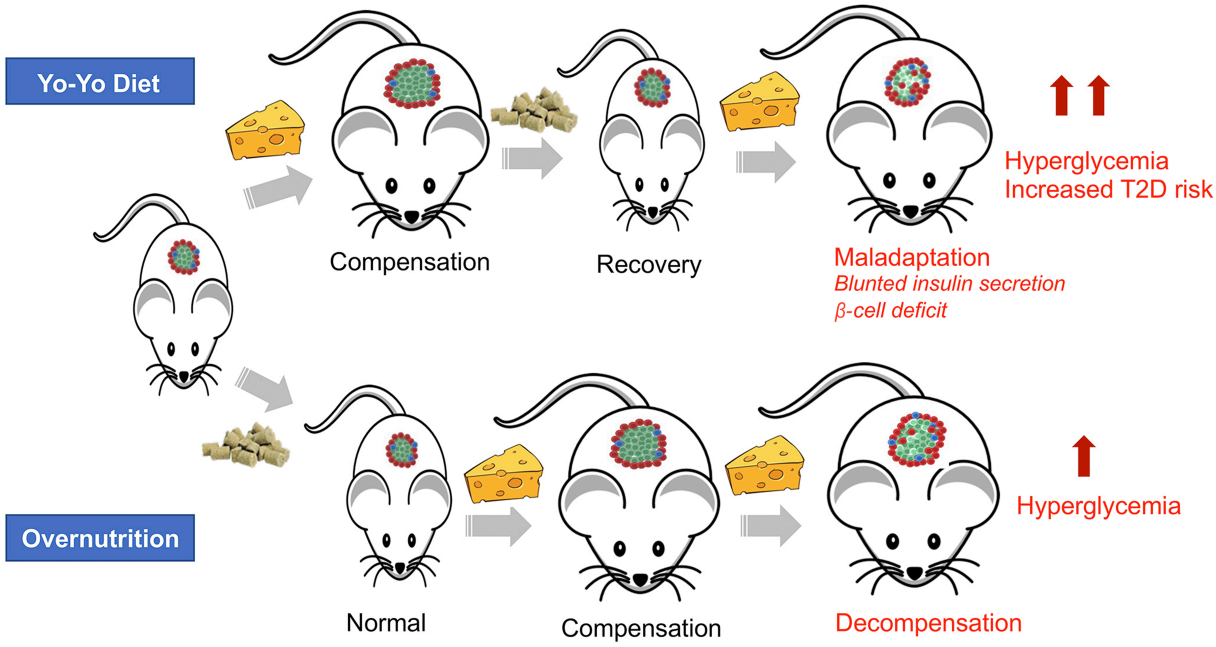

Figure 1—Weight cycling and β-cell homeostasis. Mice exposed to a weight cycling or yo-yo diet have blunted insulin secretion, reduced β-cell mass, and compromised mature β-cell identity compared with similarly obese mice. This leads to aggravated hyperglycemia and creates a maladaptive state, predisposing mice to an elevated risk of T2D.

weight cycling will identify the signaling molecules contributing to β-cell maladaptation, either directly or through tissue cross talk. Given the regulatory importance of diurnal nutrient cycles and cell-intrinsic metabolic oscillations in β-cell function (12,13), it is important to define the mechanisms by which β-cells adapt to repeated nutrient variations. Furthermore, in light of the balance between mTORC1 and AMPK activity in β-cell metabolic adaptation (14,15), these nutrient-sensing mechanisms may modulate the adaptive and maladaptive responses to drastic nutrient fluctuations induced by weight cycling.

The adaptation of cellular response to changing nutrient cues at the transcriptional level involves the epigenome. Epigenetic dysregulation has been identified as a major player underlying β-cell defects as well as the dysfunction of peripheral insulin-sensitive tissues in diabetes (16–18). Chronic exposure to a particular metabolic state (such as hyperglycemia) can induce irreversible epigenetic and functional changes that persist even after cessation of the exposure (19). This phenomenon of "metabolic memory" could be pertinent to adverse outcomes associated with weight cycling. Notably, a recent study suggested that the timing of dietary intervention is critical in shaping the β-cell response. A dietary switch to induce weight loss prevented obesity-related β-cell epigenetic programming and functional defects if incorporated prior to the onset of β-cell decompensation (20). Mapping the epigenomic changes in β-cells and peripheral tissues may shed light on the epigenetic program and the relevant temporal window that fosters metabolic memory in response to weight cycling.

Accumulating evidence suggests the existence of an autoregulatory adaptive mechanism or "famine reaction" that predisposes to obesity following a period of starvation (21). The current study highlights the underappreciated adverse impact of yo-yo dieting on islet physiology that exacerbates diabetes risk. To leverage these findings for safe and effective weight management, future studies are needed to dissect the underlying mechanisms and define the impact of the extent, duration, and frequency of weight cycling on cardiometabolic outcomes. These new findings also caution against extreme interventions in patients with obesity with inevitable weight cycling that may hasten rather than prevent diabetes. With the future studies it will spur, this investigation provides a basis for close monitoring of islet function in subjects undergoing weight interventions to minimize the metabolic risk.

Funding. K.M. is supported by a grant from the National Institutes of Health (R01DK112794) and an Arthur Riggs Diabetes and Metabolism Institute Pilot Project. S.D. is supported by a grant from the National Institutes of Health (R01DK120523), a Human Islet Research Network New Investigator Award (subaward to S.D. via UC4DK104162), an Arthur Riggs Diabetes and Metabolism Institute Pilot Project, and start-up support from City of Hope.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Paisey R, Daniels C, Howitt W, et al. Body weight, diabetes incidence vascular events and survival 15 years after very low calorie diet in community medical clinics in the UK. BMJ Nutr Prev Health 2022;5:55–61

2. Delahanty LM, Pan Q, Jablonski KA, et al.; Diabetes Prevention Program Research Group. Effects of weight loss, weight cycling, and weight loss maintenance on diabetes incidence and change in cardiometabolic traits in the Diabetes Prevention Program. Diabetes Care 2014;37:2738–2745
3. Winn NC, Cottam MA, Bhanot M, et al. Weight cycling impairs pancreatic insulin secretion but does not perturb whole-body insulin action in mice with diet-induced obesity. Diabetes 2022;71:2313–2330
4. Anderson EK, Gutierrez DA, Kennedy A, Hasty AH. Weight cycling increases T-cell accumulation in adipose tissue and impairs systemic glucose tolerance. Diabetes 2013;62:3180–3188
5. Weir GC, Bonner-Weir S. Five stages of evolving beta-cell dysfunction during progression to diabetes. Diabetes 2004;53(Suppl. 3):S16–S21
6. Weir GC, Laybutt DR, Kaneto H, Bonner-Weir S, Sharma A. Beta-cell adaptation and decompensation during the progression of diabetes. Diabetes 2001;50(Suppl. 1):S154–S159
7. Meier JJ, Ritzel RA, Maedler K, Gurlo T, Butler PC. Increased vulnerability of newly forming beta cells to cytokine-induced cell death. Diabetologia 2006;49:83–89
8. Ritzel RA, Butler PC. Replication increases beta-cell vulnerability to human islet amyloid polypeptide-induced apoptosis. Diabetes 2003;52:1701–1708
9. Ochner CN, Barrios DM, Lee CD, Pi-Sunyer FX. Biological mechanisms that promote weight regain following weight loss in obese humans. Physiol Behav 2013;120:106–113
10. Grenier-Larouche T, Carreau AM, Geloën A, et al. Fatty acid metabolic remodeling during type 2 diabetes remission after bariatric surgery. Diabetes 2017;66:2743–2755
11. Prentki M, Peyot ML, Masiello P, Madiraju SRM. Nutrient-induced metabolic stress, adaptation, detoxification, and toxicity in the pancreatic β-cell. Diabetes 2020;69:279–290
12. Lee J, Moulik M, Fang Z, et al. Bmal1 and β-cell clock are required for adaptation to circadian disruption, and their loss of function leads to oxidative stress-induced β-cell failure in mice. Mol Cell Biol 2013;33:2327–2338
13. Merrins MJ, Corkey BE, Kibbey RG, Prentki M. Metabolic cycles and signals for insulin secretion. Cell Metab 2022;34:947–968
14. Jaafar R, Tran S, Shah AN, et al. mTORC1 to AMPK switching underlies β-cell metabolic plasticity during maturation and diabetes. J Clin Invest 2019;129:4124–4137
15. Esch N, Jo S, Moore M, Alejandro EU. Nutrient sensor mTOR and OGT: orchestrators of organelle homeostasis in pancreatic β-cells. J Diabetes Res 2020;2020:8872639
16. Parveen N, Dhawan S. DNA methylation patterning and the regulation of beta cell homeostasis. Front Endocrinol (Lausanne) 2021;12:651258
17. Ling C, Bacos K, Rönn T. Epigenetics of type 2 diabetes mellitus and weight change—a tool for precision medicine? Nat Rev Endocrinol 2022;18:433–448
18. Lu TT, Heyne S, Dror E, et al. The polycomb-dependent epigenome controls β cell dysfunction, dedifferentiation, and diabetes. Cell Metab 2018;27:1294–1308.e7
19. Reddy MA, Zhang E, Natarajan R. Epigenetic mechanisms in diabetic complications and metabolic memory. Diabetologia 2015;58:443–455
20. Wang RR, Qiu X, Pan R, et al. Dietary intervention preserves β cell function in mice through CTCF-mediated transcriptional reprogramming. J Exp Med 2022;219:e20211779
21. Dulloo AG. Physiology of weight regain: lessons from the classic Minnesota Starvation Experiment on human body composition regulation. Obes Rev 2021;22(Suppl. 2):e13189